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Platinum(II) non-covalent crosslinkers for supramolecular DNA hydrogels†

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Manipulation of non-covalent metal–metal interactions allows the fabrication of functional metallosupramolecular structures with diverse supramolecular behaviors. The majority of reported studies are mostly designed and governed by thermodynamics, with very few examples of metallosupramolecular systems exhibiting intriguing kinetics. Here we report a serendipitous finding of platinum(II) complexes serving as non-covalent crosslinkers for the fabrication of supramolecular DNA hydrogels. Upon mixing the alkynylplatinum(II) terpyridine complex with double-stranded DNA in aqueous solution, the platinum(II) complex molecules are found to first stack into columnar phases by metal–metal and π – π interactions, and then the columnar phases that carry multiple positive charges crosslink the negatively charged DNA strands to form supramolecular hydrogels with luminescence properties and excellent processability. Subsequent platinum(II) intercalation into DNA competes with the metal–metal and π – π interactions at the crosslinking points, switching on the spontaneous gel-to-sol transition. In the case of a chloro (2,6-bis(benzimidazol-2'-yl)pyridine)platinum(II) complex, with [Pt(bzimpy)Cl]⁺ serving as a non-covalent crosslinker where the metal–metal and π – π interactions outcompete platinum(II) intercalation, the intercalation-driven gel-to-sol transition pathway is blocked since the gel state is energetically more favorable than the sol state. Interestingly, the ligand exchange reaction of the chloro ligand in [Pt(bzimpy)Cl]⁺ with glutathione (GSH) has endowed the complexes with enhanced hydrophilicity, decreasing the planarity of the complexes, and turning off the metal–metal and π – π interactions at the crosslinking points, leading to GSH-triggered hydrogel dissociation.

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Introduction

Platinum(II) polypyridine complexes of d⁸ electronic configuration and square-planar geometry have attracted growing attention because of their intriguing spectroscopic and luminescence properties, as well as their diverse supramolecular behaviors associated with non-covalent metal–metal and π – π interactions.¹ These platinum(II) complexes can form highly ordered extended linear chains or oligomeric structures and display rich polymorphism in the solid state.^{1,2} Metal–metal and π – π interactions serve as the main driving force to induce the aggregation of platinum(II) complexes in the solution state and direct the fabrication of platinum(II) supramolecular assemblies such as molecular architectures,³ liquid crystals⁴ and well-defined nanostructures.⁵ Polyelectrolytes are also found to interact with platinum(II) complexes electrostatically and induce the aggregation of platinum(II) complexes *via* metal–metal and π – π interactions, giving rise to drastic UV-vis absorption and luminescence changes.⁶ When coupled to

chemical reactions, these polyelectrolyte-induced aggregation systems have been used for chemo/biosensing applications, but neither well-defined nanostructures nor metallosupramolecular gels have been observed in these systems.⁶ The covalent tethering of platinum(II)–polypyridine units to block copolymers can produce pH- or temperature-responsive metallopolymers, whereas formation of metallosupramolecular gels has not been observed so far in such systems.⁷ The fabrication of supramolecular gels of platinum(II) complexes *via* metal–metal and π – π stacking interactions in both organic and aqueous media has also been observed.⁸ To date, the stimuli-responsive behaviors of these platinum(II) supramolecular gels in reported studies remain limited to thermal responsiveness.⁸

The manipulation of non-covalent metal–metal interactions has been demonstrated to be an efficient pathway for the fabrication of metallosupramolecular structures and the modulation of their supramolecular behaviors and functions.^{1–8} The majority of the reported metallosupramolecular systems are designed and governed by thermodynamics, with supramolecular systems involving pathway complexity and fuel-driven processes that exhibit intriguing kinetics much less reported (*vide infra*).

Investigation and control of kinetics in supramolecular systems have emerged as an important topic in supramolecular

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bis(benzimidazol-2'-yl)pyridine)platinum(II) complex, with $[\text{Pt}(\text{bzimpy})\text{Cl}]^+$ serving as a non-covalent crosslinker where the metal-metal and π - π interactions outcompete platinum(II) intercalation, the intercalation-driven gel-to-sol transition pathway is blocked since the gel state is energetically more favorable than the sol state. Interestingly, the ligand exchange reaction of the chloro ligand in $[\text{Pt}(\text{bzimpy})\text{Cl}]^+$ with glutathione (GSH) has endowed the complexes with enhanced hydrophilicity, decreasing the planarity of the complexes, and turning off the metal-metal and π - π interactions at the crosslinking points, leading to GSH-triggered hydrogel dissociation.

Platinum(II) complexes as non-covalent crosslinkers for supramolecular DNA hydrogels

Complex 1

Complex 2

Complex 3

Complex 4

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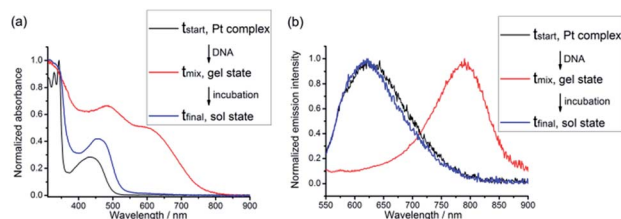


Fig. 1 (a) UV-vis absorption and (b) steady-state emission spectral changes of the supramolecular system of complex **1** (0.15 mM) and smDNA ([base pair] = 1.35 mM) during the transformation from platinum(II) monomers through the platinum(II)-DNA gel state to the platinum(II) intercalation sol state.

solution shows a red shift of the absorption band with respect to complex **1** in acetonitrile (Fig. 1a), while its emission spectrum shows a typical triplet metal-to-ligand charge transfer ($^3\text{MLCT}$) emission band similar to that of complex **1** in acetonitrile solution (Fig. 1b). According to literature reported studies,^{14,14} these observations suggest the intercalation of the platinum(II) complex molecules into double-stranded DNA in the final yellow solution. The transient presence of the gel-like precipitates and the intriguing transformation of platinum(II) complexes from monomeric forms through aggregation into intercalated forms have motivated us to investigate the structure and the formation mechanism of these gel-like precipitates and the gel-to-sol transition behaviors of the platinum(II)-DNA supramolecular system.

Hydrogels can be obtained with an isolation yield of approximately 70% by mixing complex **1** (1 mg mL⁻¹) and smDNA (1 mg mL⁻¹) in aqueous solution at a platinum(II)/base pair molar ratio of 1 : 1 (see the Experimental section in the ESI†). After isolation from the assembly mixture, the hydrogels are found to be stable in water. The **1**-DNA gel has a water content of approximately 90% and exhibits a fibrous network structure under TEM observation (*vide infra*). No hydrogel formation is observed when complex **1** with a concentration below 0.1 mM is mixed with smDNA at a platinum(II)/base pair molar ratio of 1 : 1. Another alkynylplatinum(II) terpyridine complex **2** and [Pt(bzimpy)Cl]⁺ complexes **3a**, **3b** and **4** also show hydrogel formation when mixed with aqueous solutions of smDNA. Fig. 2a shows that star-shaped hydrogels of complex **3a** and smDNA can be obtained with tailorable sizes by using a silicone mold. The red hydrogels can be encapsulated by agarose hydrogels to form core-shell star-shaped hydrogels (Fig. 2b and c), which display red emission under 365 nm UV irradiation (Fig. 2d).

The UV-vis absorption spectra of the platinum(II)-DNA hydrogels, **1**-DNA gel and **2**-DNA gel, show the emergence of low-energy MMLCT absorption bands with peak maxima at 603 nm and 564 nm, respectively, as well as new low-energy $^3\text{MMLCT}$ emission bands at 791 nm and 749 nm in the emission spectra, respectively (Fig. 3a and b).^{5f,6a} For **3a**-DNA gel and **4**-DNA gel, low-energy MMLCT absorption bands appear in the region of 470 to 630 nm in the UV-vis absorption spectra, and their emission spectra exhibit low-energy $^3\text{MMLCT}$ emission bands with peak maxima at 645 nm and 674 nm, respectively (Fig. 3c and d).¹⁵

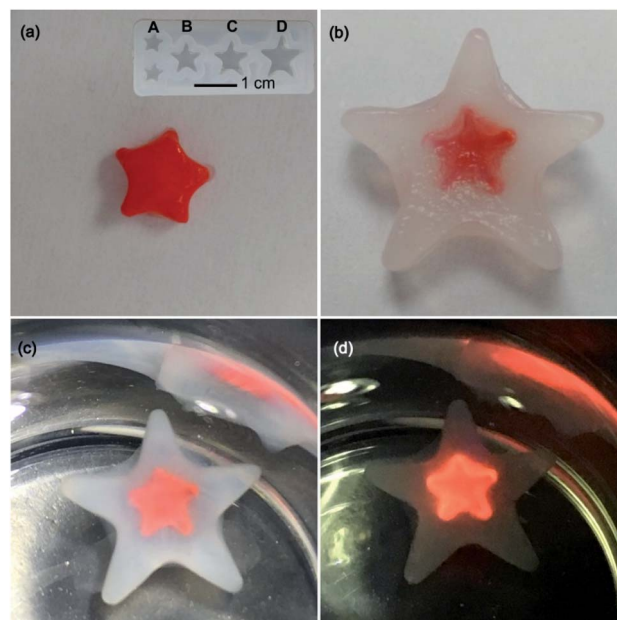


Fig. 2 (a) A star-shaped **3a**-DNA gel prepared by using silicone mold A. (b) A core-shell star-shaped hydrogels prepared by cooling a hot agarose solution in the presence of **3a**-DNA gel in silicone mold D. (c and d) The core-shell star-shaped hydrogels in water under ambient light (c) and under 365 nm UV irradiation (d). Inset in (a) shows the star-shaped silicone molds A-D with different sizes.

TEM images show that **1**-DNA gel and **2**-DNA gel possess fibrous network structures (Fig. 4a and d). The weight percentages of platinum elements in the dried gel have been determined by inductively coupled plasma-mass spectrometry (ICP-MS) to be 5% and 7% for **1**-DNA gel and **2**-DNA gel, respectively. These results indicate that DNA strands are the major component and consist of a continuous phase in the platinum(II)-DNA hydrogels. Selected area electron diffraction (SAED) study of a fibrous network of **1**-DNA gel shows a ring-like

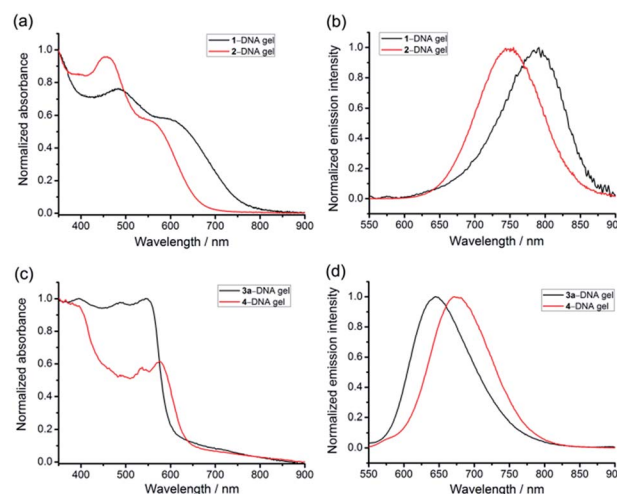
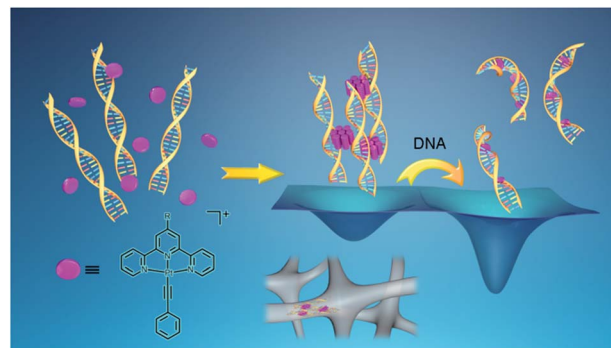


Fig. 3 (a and c) UV-vis absorption and (b and d) steady-state emission spectra of the platinum(II)-DNA hydrogels in the dried state.





Scheme 2 Supramolecular system of alkynyl(platinum(II)) terpyridine complexes and double-stranded DNA. The wells represent the qualitative energy profile of the system. In the platinum(II)–DNA system at a complex 1/base pair molar ratio of 1 : 9, upon the mixing of complex 1 and DNA aqueous solution, the platinum(II) complexes are found to first stack into columnar phases and then non-covalently crosslink the DNA strands by electrostatic attractions. Subsequently, due to the presence of excessive DNA in the assembly mixture, platinum(II) intercalation into DNA base pairs can compete with non-covalent metal–metal and π – π interactions between the platinum(II) complexes at the crosslinking points of the hydrogels, switching on the spontaneous transition from the off-pathway gel state to the on-pathway sol state. The platinum(II) stacking and electrostatic crosslinking are kinetically favored, while the platinum(II) intercalation into DNA base pairs is thermodynamically stable.

150 mM NaCl at room temperature. In contrast, the as-formed hydrogels of the alkynylplatinum(II) terpyridine complex and DNA show transient presence in the assembly mixture where DNA is in excess as shown in Fig. 1. To study the spontaneous sol-to-gel transformation in detail, freshly purified hydrogels of the alkynylplatinum(II) terpyridine complex and smDNA have been immersed in fresh smDNA solution at room temperature (see the Experimental section). The colorless smDNA solution gradually turns yellow due to the release of platinum(II) complexes from the hydrogels. *In situ* UV-vis spectra of the yellow solutions show the increase of absorption bands at 452 nm and 444 nm for 1-DNA gel and 2-DNA gel, respectively, with the increase of incubation time (Fig. 5). The 1-DNA gel and 2-DNA gel have a half-life of 8 min and 14 min in smDNA solution, respectively. The $-\text{OC}_6\text{H}_{13}$ moiety on the platinum(II) complexes can provide additional hydrophobic stabilizing

Fig. 5 UV-vis absorption spectral changes of (a) 1-DNA gel and (b) 2-DNA gel upon incubation in 0.5 mg mL⁻¹ smDNA at room temperature. Insets show the plots of UV-vis absorption at 452 nm and 444 nm *versus* incubation time for (a) 1-DNA gel and (b) 2-DNA gel, respectively.

non-covalent metal-metal and π - π interactions between the platinum(II) complexes at the crosslinking points of the hydrogels, switching on the spontaneous transition from the off-pathway gel state to the on-pathway sol state (Scheme 2). The platinum(II) stacking and electrostatic crosslinking are kinetically favored, while the platinum(II) intercalation into DNA base pairs is thermodynamically stable. The hydrogel formation and subsequent gel-to-sol transition exhibit pathway complexity in the platinum(II)-DNA supramolecular system, which have not been observed before in metallosupramolecular systems.

The stability of platinum(II)-DNA hydrogels, **3a**-DNA gel, **3b**-DNA gel and **4**-DNA gel, in DNA solution has also been tested, and it turns out that these [Pt(bzimpy)Cl]⁺-DNA hydrogels are kept intact by incubation of the hydrogels in smDNA solution at room temperature for one week. Spectroscopic studies indicate the absence of platinum(II) intercalation in the [Pt(bzimpy)Cl]⁺-DNA supramolecular systems (Text S2 and Fig. S2 in the ESI†).¹⁵ In the case of [Pt(bzimpy)Cl]⁺ complexes as non-covalent crosslinkers, although the DNA is in excess, the strong tendency for the formation of metal-metal and π - π interactions between [Pt(bzimpy)Cl]⁺ complexes due to their large π -surface, as well as the additional hydrophobic interactions of C₁₂ alkyl chains on complex **4**, can outcompete the platinum(II) intercalation into DNA base pairs. Therefore, the gel state in the [Pt(bzimpy)Cl]⁺-DNA systems is energetically more favorable than the sol state, which can explain the enhanced stability of the [Pt(bzimpy)Cl]⁺-DNA hydrogels in DNA solution. These observations suggest that the intercalation-driven gel-to-sol transition pathway can be switched on or off by rational design of the metal complexes in supramolecular systems.

Platinum(II) is one of the soft metal centers with a high binding affinity towards thiol. The endogenous thiol-containing molecule, glutathione (GSH), exists at a concentration of up to approximately 10 mM in animal cells and is often overproduced in tumor microenvironments.¹⁶ GSH has been frequently employed as a redox stimuli trigger in reported studies,^{16b,17} while the utilization of GSH based on platinum(II)-thiol coordination in tuning material properties has been much less explored.

The stability of the $[\text{Pt}(\text{bzimpy})\text{Cl}]^+$ -DNA hydrogels in aqueous solution of GSH has been investigated (Fig. 7). ICP-MS measurements show a gradual release of platinum from **3b**-DNA gel upon incubation of the hydrogels in 10 mM GSH aqueous solution. Conversely, in the control experiment, **3b**-DNA gel does not show any platinum release after incubation in pure water for one week. Gradual platinum release has also been observed by ICP-MS upon incubation of **3a**-DNA in 10 mM GSH solution. **3a**-DNA is also stable in pure water. Interestingly, **4**-DNA gel incorporated with C_{12} alkyl chains on $[\text{Pt}(\text{bzimpy})\text{Cl}]^+$ complexes has been found to show insignificant platinum release in both pure water and 10 mM GSH solution. Besides, **2**-DNA gel of alkynylplatinum(II) terpyridine complexes is also found to be stable in 10 mM GSH solution. These observations indicate that the stability of platinum(II)-DNA hydrogels in GSH

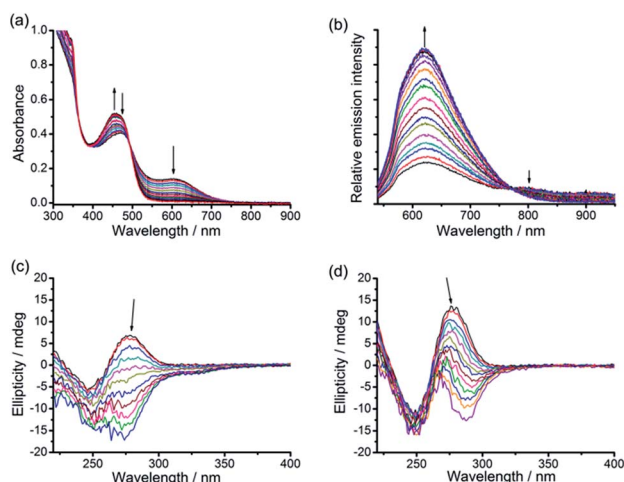


Fig. 6 (a) UV-vis absorption and (b) steady-state emission ($\lambda_{\text{ex}} = 492$ nm) spectral changes of the **1**-DNA supramolecular system ($[\text{complex } \mathbf{1}] = 0.15$ mM) upon DNA titration at DNA base pair/platinum(II) molar ratios from 1.7 to 4.2. (c and d) CD spectral changes of DNA with increasing platinum(II)/base pair molar ratio from 0 to 0.3 in **1**-DNA (c) and **2**-DNA (d) supramolecular systems.

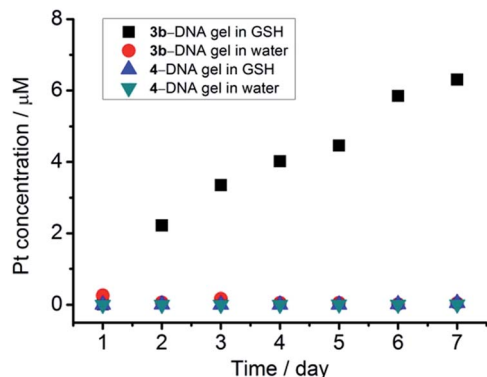


Fig. 7 Platinum release from $[\text{Pt}(\text{bzimpy})\text{Cl}]^+$ -DNA hydrogels by incubation of the hydrogels in 10 mM GSH aqueous solution at room temperature.

solution can be modulated by the structure of the platinum(II) complexes.

Since GSH cannot react with smDNA in aqueous solution, NMR experiments of the **3a**-GSH reaction system in D_2O were performed (Fig. 8, Text S3, Fig. S3 and S4 in the ESI†) to investigate the mechanism of GSH-triggered dissociation of the $[\text{Pt}(\text{bzimpy})\text{Cl}]^+$ -DNA hydrogels. The new peaks at δ 2.61 ppm and 2.82 ppm in the ^1H NMR spectrum of the purified product from **3a**-GSH reaction mixture that can be assigned to β -Cys protons (Fig. 8a), together with the large downfield shift of β -Cys carbon from δ 25.3 ppm to 33.6 ppm in the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum (Fig. 8b), indicated the involvement of the sulfur in the coordination of GSH to platinum(II). The $^{195}\text{Pt}\{^1\text{H}\}$ NMR spectrum with a peak at δ -3063 ppm (ref. 18) and the HR ESI



Fig. 8 (a) ^1H NMR, (b) $^{13}\text{C}\{^1\text{H}\}$ NMR and (c) $^{195}\text{Pt}\{^1\text{H}\}$ NMR spectra of the **3a**-GSH reaction system in D_2O .



Scheme 3 Supramolecular system of $[\text{Pt}(\text{bzimpy})\text{Cl}]^+$ and double-stranded DNA. The platinum(II) complexes stack into columnar phases and then non-covalently crosslink the DNA strands by electrostatic attractions to form hydrogels. In GSH aqueous solution, the ligand exchange reaction of the chloro ligand in $[\text{Pt}(\text{bzimpy})\text{Cl}]^+$ with GSH endows the complexes with enhanced hydrophilicity, decreasing the planarity of the complexes, and turning off the metal-metal and π - π interactions at the crosslinking points, leading to energetically unfavorable hydrogel dissociation. The wells represent the qualitative energy profile of the system.

mass spectra of the reaction mixture further confirmed the platinum(II)-thiol coordination (Fig. 8c and S5 in the ESI†), that is, the ligand exchange reaction of the chloro ligand in complex **3a** with glutathione. The emergence of a set of signals in the region of aromatic protons in both ^1H NMR and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra (Fig. 8a and b), when compared to the NMR spectrum of complex **3a** in D_2O (Fig. 8a), indicated the deaggregation of the platinum(II) complexes due to the enhanced hydrophilicity provided by the GS moiety after platinum(II)-thiol coordination.

When the aqueous solution of $[\text{Pt}(\text{bzimpy})(\text{GS})]^+$ (the purified product from the **3a**-GSH reaction mixture) is mixed with smDNA, no hydrogel formation is observed. Therefore, in the case of **3a**-DNA gel, it is the ligand exchange reaction of the chloro ligand in $[\text{Pt}(\text{bzimpy})\text{Cl}]^+$ with GSH that endows the complex molecules with enhanced hydrophilicity, decreases the



Scheme 4 Schematic diagram showing platinum(II) non-covalent crosslinkers for supramolecular DNA hydrogels. By varying the structures of the platinum(II) non-covalent crosslinkers, as well as the incorporation of platinum(II) intercalation and ligand exchange reactions into the systems, supramolecular DNA hydrogels with controlled kinetic properties and tunable gel-to-sol transition behaviors have been produced. The wells represent the qualitative energy profile of the system.

of metal complexes, the supramolecular DNA hydrogels may exhibit promising characteristics for biomedical applications.

There are no conflicts to declare.

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In summary, the present study shows a serendipitous finding of platinum(II) non-covalent crosslinkers for the fabrication of supramolecular DNA hydrogels with controlled kinetic properties and tunable gel-to-sol transition behaviors (Scheme 4). Upon mixing the alkynylplatinum(II) terpyridine complex with double-stranded DNA in aqueous solution, the platinum(II) complexes have been found to first stack into columnar phases by metal-metal and π - π interactions, and then the platinum(II) columnar phases that carry multiple positive charges crosslink negatively charged DNA chains by electrostatic attractions to form supramolecular hydrogels with luminescence properties and excellent processability. Subsequently, platinum(II) intercalation into DNA competes with the metal-metal and π - π interactions between the platinum(II) complexes at the cross-linking points of the supramolecular DNA hydrogels, switching on the spontaneous transition from the off-pathway gel state to the on-pathway sol state (Scheme 4). The rate of the gel-to-sol transition has been found to decrease with the hydrophobicity of the alkynylplatinum(II) terpyridine complexes in the hydrogels. With $[\text{Pt}(\text{bzimpy})\text{Cl}]^+$ as a non-covalent crosslinker where the metal-metal and π - π interactions are stronger than platinum(II) intercalation, the gel state is energetically more favorable than the sol state, and thus the intercalation-driven gel-to-sol transition pathway can be blocked. Interestingly, the ligand exchange reaction of the chloro ligand in $[\text{Pt}(\text{bzimpy})\text{Cl}]^+$ with GSH has been found to endow the complexes with enhanced hydrophilicity, decreasing the planarity of the complexes, and turning off the metal-metal and π - π interactions at the cross-linking points, leading to energetically unfavorable hydrogel dissociation that is triggered by GSH (Scheme 4). The rate of GSH-triggered hydrogel dissociation has been found to decrease with the hydrophobicity of the $[\text{Pt}(\text{bzimpy})\text{Cl}]^+$ complexes. In view of the flexibility of the modular approach of the present study, the biocompatibility of the DNA matrix, as well as the intriguing luminescence properties and anti-cancer properties

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